

## Highlights

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**Table 1. Guidelines for CKD-MBD(6)**

	KDIGO 2009 (3)	KDOQI 2003(7)
Monitoring biochemical components	Start at CKD 3. Include Ca, Phos, PTH, ALP	Same but no comment on ALP
Goal Phos	CKD 3–4: normal CKD 5: toward normal	CKD 3–4: normal CKD 5: 3.5 to 5.5
Goal Ca	Normal Suggest to stay away from CaxPhos	CKD 3–4: normal CKD 5: 8.4–9.5 CaxPhos <55
Goal PTH	CKD 3–4: unknown CKD 5: 2 to 9 times upper limit of normal. When PTH above upper limits of normal evaluate correctable factors like Phos, Ca, Vit D	CKD 3: 35–70 pg/mL CKD 4: 70–110 pg/mL CKD 5: 150–300 pg/mL
Goal 25(OH) Vit D	Start at CKD 3. Correct as in general population	CKD 3–4, measure only if PTH is above target. Replace if <30 ng/mL
PTH assay	Clinical labs should report assay method handling and sampling. Recommend 2nd generation assay	Recommendation based on 2nd generation Nichols Allegro assay currently unavailable
Bone-specific ALP	Suggest testing bone-specific ALP in certain individuals and very high or low levels predict underlying bone turnover	No specific suggestions
Bone biopsy	Reasonable in various settings and prior to bisphosphonates in CKD-MBD	Should be considered
BMD	Not recommended routinely in CKD 3–5 with biochemical abnormalities	DEXA should be measured in patients with fracture and osteoporosis risk
Vascular calcification	No recommendation for routine screening	same

Abbreviations: ALP = alkaline phosphatase; Ca = calcium; CaxPhos = product of serum calcium and phosphorus; CKD = chronic kidney disease; DEXA = dual-energy X-ray absorptiometry; KDIGO = Kidney Disease: Improving Global Outcomes; KDOQI = Kidney Disease Outcomes Quality Initiative; MBD = mineral and bone disorder; Phos = phosphorus; PTH = parathyroid hormone; Vit D = vitamin D.

## KDIGO Glomerulonephritis Guideline

By Daniel Cattran

Glomerulonephritis (GN)—including both primary and secondary variants in aggregate—remains one of the most common types of kidney disease that progresses to end stage renal disease (ESRD). However, this fact alone seriously underestimates the extent of the problem associated with GN. Many cases of the disease begin early in life and can have a devastating effect both on the individual and their families. The disease process is often slowly progressive and therefore its devastating impact on the individual’s physical growth, educational opportunities, quality of life, and eventual societal productivity is rarely taken into account when assessing the impact of these disorders.

The variants of GN included in the Kidney Disease: Improving Global Outcomes (KDIGO) GN guideline are classified as orphan diseases because of their rarity. This—in combination with their long clinical course, punctuated with remissions and relapses, and very large variation in treatment responsiveness—makes tracking them difficult. A recent *Kidney International* editorial, entitled *Glomerular Disease: Why Is There a Dearth of High-quality Clinical Trials*, further delineates these problems (1). The authors proposed that the GN guidelines developed under the auspices of a global nonprofit foundation KDIGO would help by encouraging a uniform classification system of diseases and common clinical end points as well as utilizing an evidence-based review process to establish clinical practice guidelines for glomerulonephritis. These guidelines were published as a *Kidney International* supplement in June 2012 (2).

Clinical practice guidelines (CPGs) have become an important element in clinical practice and can now be found in virtually every branch of medicine. The Institute of Medicine defines CPGs as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” (3). The potential benefits of CPGs include providing clear recommendations based on currently available evidence, thereby potentially improving the quality of clinical decisions. The advantage of the physician knowing the specific circumstances surrounding the individual patient cannot be underestimated in the final judgment about treatment. Ideally, decisions take into account the physician’s experience and acumen as well as the individual patient characteristics and opinion as well as the evidence. The KDIGO GN guideline was purposely developed to have potential global application. This implies that it takes into account not only the different financial situations at the individual level, but also the social and economic realities of

the underlying health care system.

The development of the GN guideline was a lengthy process and took several years. The Work Group consisted of both experienced and expert clinicians and an evidence review team trained in the complex field of guideline development. The Work Group formulated recommendations related to a specific question or topic with each set of recommendations followed by a rationale section summarizing the evidence and the reasoning for each recommendation, and explaining why specific wording was chosen. It is critical to understand the grading process in the KDIGO GN guideline. Each recommendation has both an alphabetical and numeric code. The alphabetical code (A, B, C, and D) indicates the quality of the evidence supporting the recommendation or suggestion, whereas the numeric grade (1 or 2) denotes the strength of the evidence. At a practice level, level 1 generally means a recommendation that this course of action should be instituted, whereas level 2 is more compatible with a suggestion that requires that each affected individual needs careful consideration and that different choices may be appropriate for different patients. This provides a range of recommendations from 1A (the highest recommendation) to 2D (the lowest), with the latter usually reflecting the considered opinion of the GN Work Group.

No matter what the grading, the ultimate physician decision always requires consideration in regards to the balance between the risks and benefits of treatment. Ideally, the chosen treatment regimen reduces the total exposure to immunosuppressive therapy yet still results in the minimization of immediate morbidity (e.g., achieving remission of nephrotic syndrome) and prevents disease progression. The total exposure risk, however, must always be balanced against the alternatives (i.e., potential progression to ESRD with its associated shortened life span, and/or a renal transplant with its absolute requirement of continuous immunosuppression). This has modified the physician stance in favor of more intensive and prolonged treatment in the more chronic GN variants—for example, lupus nephritis, vasculitis, focal segmental glomerulosclerosis (FSGS), and even membranous nephropathy—given the alternative. In addition, the recognition that the clinical equivalent of control is often reduction in proteinuria versus cure defined by permanent complete remission of proteinuria has resulted in the concept of “maintenance” therapy in many of these disorders. This paradigm shift in management has translated into the use of more extended (or repeated) treatment regimens with the inevitable cor-

ollary of more toxic drug exposure.

The KDIGO GN guideline is intended to provide the practitioner with information to make an informed decision based on the data available for most of the common glomerular diseases. The important point here is that the CPGs are intended to provide guidance rather than a strict set of rules. The overarching purpose of the recommendations is to assist in decision making and not provide a “cookie-cutter” approach to management. A guideline recommendation/suggestion cannot account for all possible variations of patients, providers, and system factors. Thus, each health care provider needs to assess the appropriateness of a particular recommendation or suggestion within a specific context.

The scope of this GN CPG is limited to the treatment phase of patients already diagnosed with GN. It includes the most common primary histologic variants as well as those associated with systemic disease. It does not cover diagnosis or prevention of GN. The guideline addresses the following forms of GN: steroid-sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS) in children; minimal change disease and idiopathic FSGS in children and adults; idiopathic membranous nephropathy; idiopathic membranoproliferative GN; GN associated with infections, immunoglobulin A nephropathy, and Henoch-Schonlein purpura nephritis; lupus nephritis; renal vasculitis; and anti-glomerular basement membrane GN.

Treatment approaches are addressed in each chapter and the guideline recommendations are based on systematic reviews of relevant trials. All materials, including evidence tables and evidence profiles, and general management issues not included in the *Kidney International* supplement are available online at <http://www.kdigo.org/>. Limitations of the evidence are discussed and specific suggestions are provided for future research.

This guideline was written primarily for nephrologists, although the broader health care profession—including other physicians, nurses, pharmacists, and health care professionals who care for patients with GN—will hopefully find it educational and of interest. This guideline was not written directly for patients or caregivers, although certain extracted and well explained elements of the GN guideline would potentially provide useful information.

Prior to specific recommendations on each of the GN types, there is a chapter on the general principles in management of glomerular diseases, including assessment of kidney function, outcome measures, and impact of age, sex, ethnicity, and genetic background—all relevant issues that come into play at the interface between the individual patient and their physician. Management of complications of GN, treatment costs, and other related issues are also touched on in this chapter.

In a recent *Kidney International* article we further explored the critical re-

lationship between GN guideline and their application at a practice level (4). This was done within a case context using specific types of glomerular disease (FSGS, membranous nephropathy, and vasculitis) to underline the relevance of the complex interaction of multiple factors that often impact treatment decisions in GN.

The purpose was to define the strains of as well as the limitations of applying guidelines to individual cases in a way designed to provide guidance to the individual nephrologists when dealing with the complex GN patient. Although the literal application of the guideline is often not possible and sometimes inappropriate, what guidelines do is provide for the reader the direction to take to ensure that the correct diagnosis is made and that the balance between the risks and benefits of specific immunosuppressive is considered. Examining the guideline within a specific case, for instance of FSGS, underlines the importance of separating the primary from the secondary cause of the lesion, and the need to consider the physical characteristics of the individual (e.g., age and body mass index). It goes on to discuss the potential importance of a normal serum albumin in the setting of the high-grade proteinuria. In addition, it touches on variations in histologic features, such as the degree of the foot process effacement prior to deciding on what treatment should be instituted.

In summary, it is important to remember what the KDIGO Guidelines for Glomerulonephritis can and cannot do. They will

- remind us what we know
- remind us what we do not know and they
- must be applied with clinical judgment
- will help to balance risk and benefit but they
- will not tell us what to do for every difficult patient in every situation. ●

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## KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease

By Roy D. Bloom

Hepatitis C virus (HCV) affects approximately 4 million Americans, and can trigger, share risk factors for, or result from CKD. Besides causing glomerulonephritis, HCV is associated with diabetes, a CKD precursor. End stage renal disease (ESRD) is a risk factor for HCV, transmitted via transfusions or transplantation in the era preceding its identification. The estimated HCV prevalence among U.S. CKD patients is 10 percent, several-fold higher than the general population, and is presumed to increase with CKD stage, with demographic variation. While acute infection is often subclinical, chronic HCV infection develops in most patients, leading to cirrhosis, hepatocellular carcinoma, and liver failure. Together with extrahepatic manifestations of glomerulonephritis and diabetes, these complications reduce HCV-positive CKD patient survival.

Standard antiviral therapy, until recently interferon-alpha (IFN) and ribavirin, achieved sustained response rates around 40 percent. Response rates are lower in patients infected with genotype 1, the most common HCV genotype among infected ESRD patients. Drug intolerance in CKD diminishes efficacy and IFN's immunostimulatory properties increase transplant rejection risk.

The impact of HCV across the CKD spectrum, coupled with limited preexisting recommendations, was the impetus for these guidelines. The multinational Work Group comprised general and transplant nephrologists, hepatologists, pathologists, virologists, epidemiologists, and infection control specialists, all with expertise in HCV or its consequences (1).

Statements were graded as strong (high-quality evidence, intervention “should be performed”), moderate (moderate-low quality evidence, intervention “should be considered”), or weak (low or absent quality evidence, consensus-based recommendations, intervention “suggested”). Five topics were covered: 1) detection and evaluation of HCV, 2) treatment of HCV infection, 3) prevention of HCV transmission in hemodialysis units, 4) management of HCV-infected transplant patients, and 5) diagnosis and management of HCV-associated kidney diseases.

### Guideline 1: Detection and evaluation of HCV in CKD

The Work Group suggested that viral testing be performed in pre-ESRD settings where HCV is implicated (e.g., glomerulonephritis), or in diabetics where infection predicts faster CKD progression. In ESRD, because liver enzymes correlate poorly with disease severity, and since earlier diagnosis permits timelier treatment opportunity, HCV testing should be mandatory in maintenance hemodialysis and transplant patients. Hemodialysis patient testing should be performed at time of treatment initiation or unit transfer. Given limited sensitivity of third generation serological testing in ESRD patients, high HCV prevalence facilities should consider testing patients once with nucleic acid testing, since some seronegative individuals may actually be viremic. In low-prevalence units, serological testing should suffice. Since incidence rates of new HCV infection in the United States are 3.1 percent, serological retesting of uninfected patients every 6 to 12 months should be considered. In previously uninfected patients with new/unexplained transaminitis, or whose HCV risk has changed because of new exposures, nucleic acid testing should be performed.

### Guideline 2: Treatment of HCV infection in CKD patients

Major randomized controlled trials for treating HCV have excluded CKD patients, resulting in low-quality evidence regarding therapies and indications in this population. Since HCV can cause CKD and reduce ESRD patient survival—and given the slight evidence that viral clearance improves outcomes—the Work Group felt a treatment guideline was necessary even if based on expert judgment and extrapolation from non-CKD patients. In formulating recommendations, they recognized that: 1) the natural course of HCV in CKD may differ from non-CKD populations; 2) most studies are retrospective and underpowered; 3) information on viral co-infection, mode of acquisition, liver histology, and post-treatment outcomes is sparse; and 4) many IFN-based stud-

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